Supporting Information

Practical Metal-Free Synthesis of Chalcone Derivatives via a Tandem Cross-Dehydrogenative-Coupling/Elimination Reaction

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1. Materials and Methods

General. All reactions were carried out in a flame-dried, sealed Schlenk reaction tube under an atmosphere of nitrogen or air. Analytical thin-layer chromatography was performed on glass plates coated with 0.25 mm 230–400 mesh silica gel containing a fluorescent indicator (Merck). Flash silica gel column chromatography was performed on silica gel 60N (spherical and neutral, 140–325 mesh) as described by Still. NMR spectra were measured on a Bruker AV-400 spectrometer and reported in parts per million. H NMR spectra were recorded at 400 MHz in CDCl₃ were referenced internally to tetramethysilane as a standard, and C NMR spectra were recorded at 100 MHz and referenced to the solvent resonance. Analytical gas chromatography (GC) was carried out on a Thermo Trace 1300 gas chromatograph, equipped with a flame ionization detector. Mass spectra (GC-MS, LC-MS) were taken at Thermo Trace 1300 gas chromatograph mass spectrometer or Waters TDQ/UPLC H-CLASS-SQ Detector 2. High resolution mass spectra (HRMS) were recorded by ESI-TOF.

Materials. Unless otherwise noted, materials were purchased from Tokyo Chemical Industry Co., Aldrich Inc., and other commercial suppliers and used as received. Solvents were dried over CaH₂ (for DCE and DCM) or sodium (for dioxane and THF) by refluxing for overnight and freshly distilled prior to use. tert-Amyl-OH was purchased from commercial suppliers and used directly without further purification.
2. Investigation of the Key Reaction Parameters

The reactions were performed according to the General Procedure, with the corresponding modifications shown in Table S1-S5. The crude mixture was analyzed by $^1$H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

Table S1: Investigation of the Effect of Oxidants for the Reaction$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
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<th>Temp. (°C)</th>
<th>3a (%)$^b$</th>
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<tbody>
<tr>
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<td>DCP</td>
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<td>120</td>
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<tr>
<td>3</td>
<td>TBHP</td>
<td>tert-Amyl-OH</td>
<td>120</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Ag$_2$CO$_3$</td>
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<tr>
<td>5</td>
<td>K$_2$S$_2$O$_8$</td>
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<td>50</td>
</tr>
<tr>
<td>6</td>
<td>Na$_2$S$_2$O$_8$</td>
<td>tert-Amyl-OH</td>
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<td>74</td>
</tr>
<tr>
<td>7</td>
<td>H$_2$S$_2$O$_8$</td>
<td>tert-Amyl-OH</td>
<td>120</td>
<td>94 (95)$^c$</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1a (0.25 mmol), 2d (1.25 mmol), and oxidant (3.0 equiv) in tert-Amyl-OH (0.5 mL) at 120 °C for 24 h. $^b$1H NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. $^c$Isolated yield in parentheses for 1.0 g scale synthesis.

tert-Amyl-OH = tert-Amyl alcohol.

Table S2: Investigation of the Effect of Solvent for the Reaction$^a$

<table>
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<tr>
<th>Entry</th>
<th>Oxidant</th>
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<th>Temp. (°C)</th>
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<td>Pyridine</td>
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$^a$Reaction conditions: 1a (0.25 mmol), 2d (1.25 mmol), and (NH$_4$)$_2$S$_2$O$_8$ (3.0 equiv) in solvent (0.5 mL) at 120 °C for 24 h. $^b$1H NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. $^c$Isolated yield in parentheses for 1.0 g scale synthesis.

tert-Amyl-OH = tert-Amyl alcohol; DCM = dichloromethane; DCE = 1,2-dichloroethane.

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### Table S3: Investigation of the Effect of Temperature for the Reaction\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
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<th>Temp. (°C)</th>
<th>3a (%)\textsuperscript{b}</th>
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<td>94 (95)\textsuperscript{c}</td>
</tr>
<tr>
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<td>88</td>
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\textsuperscript{a}Reaction conditions: 1a (0.25 mmol), 2d (1.25 mmol), and (NH\textsubscript{4})\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3.0 equiv) in solvent (0.5 mL) at intend temperature for 24 h. \textsuperscript{b} \textsuperscript{1}H NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. \textsuperscript{c} Isolated yield in parentheses for 1.0 g scale synthesis.

### Table S4: Investigation of the Effect of the Amount of Dibenzylamine and Oxidant for the Reaction\textsuperscript{a}

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<th>Entry</th>
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\textsuperscript{a}Reaction conditions: 1a (0.25 mmol), 2d (1.25 mmol), and (NH\textsubscript{4})\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (3.0 equiv) in solvent (0.5 mL) at 120 °C for 24 h. \textsuperscript{b} \textsuperscript{1}H NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. \textsuperscript{c} Isolated yield in parentheses for 1.0 g scale synthesis.

### Table S5: Investigation of the Source of Amines for the Reaction\textsuperscript{a}

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<td>H</td>
<td>Bn</td>
<td>Ph</td>
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<td>2f</td>
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</table>

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3. General Procedure for Metal-Free Synthesis of Chalcone Derivatives

General Procedure

In a dried Schlenk flask were placed with ketone 1 (0.5 mmol), benzylamine 2 (2.5 mmol), (NH₄)₂S₂O₈ (1.5 mmol). Then 1.0 mL of tert-Amyl-OH was added with a syringe under nitrogen atmosphere. The resulting mixture was stirred at 120 ºC for 24 h. After cooling to room temperature, the reaction mixture was diluted with 5 mL of ethyl acetate and filtered through a plug of celite, followed by with 10.0 mL of ethyl acetate. The combined organic residue was concentrated and then purified by column chromatography on silica gel to give chalcone derivative 3 (using petroleum ether/CH₂Cl₂ or petroleum ether/ethyl acetate as mobile phase).

1.0 Gram Scale Synthesis

(E)-2-methyl-1,3-diphenylprop-2-en-1-one (Table 2, 3a)

The general procedure was applied to propiophenone (1.00 g, 7.46 mmol), dibenzylamine (7.2 mL, 37.3 mmol), and (NH₄)₂S₂O₈ (5.11 g, 22.4 mmol) at 120 ºC for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 10:1--5:1) to afford the title compound as a colorless oil (1.57 g, 95% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.74 (d, J = 7.6 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.47-7.38 (m, 6H), 7.34-7.33 (m, 1H), 7.18 (s, 1H), 2.27
(E)-1-(4-chlorophenyl)-2-methyl-3-phenylprop-2-en-1-one (Table 2, 3b)

The general procedure was applied to 1-(4-chlorophenyl)propan-1-one (73 µL, 0.5 mmol), dibenzylamine (480 µL, 2.5 mmol) at 120 °C for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 5:1) to afford the title compound as a light yellow solid (113 mg, 88% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.68 (dt, J = 9.2, 2.4 Hz, 2H), 7.46-7.33 (m, 6H), 7.14 (d, J = 1.2 Hz, 1H), 2.27 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) HRMS (ESI⁺): calcd for C₁₆H₁₃ClO [M+Na]⁺ 279.0553, found 279.0554.

(E)-2-methyl-3-phenyl-1-(p-tolyl)prop-2-en-1-one (Table 2, 3c)

The general procedure was applied to 1-(p-tolyl)propan-1-one (74 µL, 0.5 mmol), dibenzylamine (480 µL, 2.5 mmol) at 120 °C for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 5:1) to afford the title compound as a colorless oil (98 mg, 83% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.68 (d, J = 7.2 Hz, 2H), 7.40 (m, 4H), 7.33 (m, 1H), 7.25 (d, J = 7.2 Hz, 2H), 7.16 (s, 1H), 2.41 (s, 3H), 2.26 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 199.3, 142.4, 141.4, 137.0, 135.9, 135.6, 129.8 (2C), 129.7 (2C), 128.9 (2C), 128.5 (3C), 21.6, 14.7. GC-MS (EI): calcd for C₁₇H₁₆O [M] 236.12, found 236.15.

(E)-1-(4-methoxyphenyl)-2-methyl-3-phenylprop-2-en-1-one (Table 2, 3d)
The general procedure was applied to 1-(4-methoxyphenyl)propan-1-one (88 µL, 0.5 mmol), dibenzylamine (480 µL, 2.5 mmol) at 120 ºC for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 5:1) to afford the title compound as a light yellow solid (110 mg, 87% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.82 (d, J = 8.8 Hz, 2H), 7.44-7.39 (m, 4H), 7.35-7.31 (m, 1H), 7.12 (s, 1H), 6.95 (d, J = 8.4 Hz, 2H), 3.87 (s, 3H), 2.27 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 198.3, 162.8, 140.1, 137.0, 136.0, 132.0, 130.7, 129.7, 128.5, 128.4, 113.6, 55.5, 15.0. GC-MS (EI): calcd for C₁₇H₁₆O₂ [M] 252.12, found 252.16.

(E)-1-(4-hydroxyphenyl)-2-methyl-3-phenylprop-2-en-1-one (Table 2, 3e)
The general procedure was applied to 1-(4-hydroxyphenyl)propan-1-one (75 mg, 0.5 mmol), dibenzylamine (480 µL, 2.5 mmol) at 120 ºC for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 5:1~5:2) to afford the title compound as a white solid (89 mg, 75% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.75 (d, J = 8.8 Hz, 2H), 7.42-7.39 (m, 4H), 7.36-7.31 (m, 1H), 7.12 (s, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.24 (brs, 1H), 2.26 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 199.3, 162.8, 140.1, 137.0, 136.0, 132.0, 130.7, 129.7, 128.62, 128.59, 115.2, 15.0. HRMS (ESI⁺): calcd for C₁₆H₁₄O₂ [M+Na]⁺ 261.0891, found 261.0900.

(E)-1,3-diphenylprop-2-en-1-one (Table 2, 3f)⁴⁵
The general procedure was applied to acetophenone (58 µL, 0.5 mmol), dibenzylamine (480 µL, 2.5 mmol) at 120 ºC for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 10:1 ~ 5:1) to afford the title compound as a light yellow solid (65 mg, 62% yield). ¹H NMR
(400 MHz, CDCl$_3$): $\delta = 8.02$ (d, $J = 7.2$ Hz, 2H), 7.80 (d, $J = 16.0$ Hz, 1H), 7.67-7.64 (m, 2H), 7.58 (tt, $J = 7.2$, 1.2 Hz, 1H), 7.57-7.49 (m, 3H), 7.44-7.41 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 190.7$, 145.0, 138.4, 135.1, 132.9, 130.7, 129.1, 128.8, 128.7, 128.6, 122.3. GC-MS (EI): calcd for C$_{15}$H$_{12}$O$_2$ [M] 208.09, found 208.14.

**Methyl 4-cinnamoylbenzoate (Table 2, 3g)**

The general procedure was applied to methyl 4-acetylbenzoate (89 mg, 0.5 mmol), dibenzylamine (480 µL, 2.5 mmol) at 120 ºC for 24 h under N$_2$. The crude product was purified by column chromatography on silica gel (petroleum ether/CH$_2$Cl$_2$ 5:1) to afford the title compound as a light yellow solid (60 mg, 43% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.17$ (d, $J = 8.4$ Hz, 2H), 8.05 (d, $J = 8.4$ Hz, 2H), 7.81 (d, $J = 15.6$ Hz, 1H), 7.67-7.65 (m, 2H), 7.49 (d, $J = 15.6$ Hz, 1H), 7.45-7.43 (m, 3H), 3.97 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 190.3$, 166.5, 146.0, 141.9, 134.8, 133.7, 131.0, 130.0, 129.2, 128.7, 128.5, 122.1, 52.6. GC-MS (EI): calcd for C$_{17}$H$_{14}$O$_3$ [M] 266.09, found 266.14.

**4-Cinnamoylbenzoic acid (Table 2, 3h)**

The general procedure was applied to methyl 4-acetylbenzoic acid (82 mg, 0.5 mmol), dibenzylamine (480 µL, 2.5 mmol) at 120 ºC for 24 h under N$_2$. The crude product was purified by column chromatography on silica gel (petroleum ether/CH$_2$Cl$_2$ 5:1~5:2) to afford the title compound as a white solid (72 mg, 54% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.23$ (d, $J = 8.4$ Hz, 2H), 8.08 (d, $J = 8.4$ Hz, 2H), 7.82 (d, $J = 15.6$ Hz, 1H), 7.68-7.65 (m, 2H), 7.50 (d, $J = 15.6$ Hz, 1H), 7.45-7.44 (m, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta = 194.2$, 171.9, 150.0, 146.0, 139.7, 139.6, 136.1, 134.8, 134.3, 134.2, 133.9, 127.2. GC-MS (EI): calcd for C$_{16}$H$_{12}$O$_3$ [M] 252.08, found 252.16.
1,2,3-Triphenylprop-2-en-1-one (Table 2, 3i and 3i')

The general procedure was applied to 1,2-diphenylethanone (91 µL, 0.5 mmol), dibenzylamine (480 µL, 2.5 mmol) at 120 ºC for 24 h under N₂. The crude product was analyzed by GC-MS using tridecane as an internal standard to get the stereoisomeric ratio (3i : 3i' = 4:1). Then, it was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 5:2) to afford the product as a white solid (3i: 27 mg, 19% yield; 3i': 7 mg, 5% yield). 

\[
\text{3i: } \delta = 7.86 (\text{dd}, J = 7.2, 1.6 \text{ Hz}, 2\text{H}), 7.54 (\text{t}, J = 4.4 \text{ Hz}, 1\text{H}), 7.44 (\text{t}, J = 7.2 \text{ Hz}, 2\text{H}), 7.35-7.32 (\text{m}, 3\text{H}), 7.29-7.28 (\text{m}, 2\text{H}), 7.23-7.16 (\text{m}, 4\text{H}), 7.29-7.16 (\text{m}, 4\text{H}), 7.09 (\text{dd}, J = 7.2, 1.6 \text{ Hz}, 2\text{H}); \]
\[
\text{13C NMR (100 MHz, CDCl}_3): \delta = 197.7, 140.8, 140.2, 138.2, 136.5, 134.8, 132.2, 130.4, 129.8, 129.7, 129.0, 128.8, 128.32, 128.29, 127.9. \]

\[
\text{3i': } \text{1H NMR (400 MHz, CDCl}_3): \delta = 8.00 (\text{dd}, J = 7.2, 1.2 \text{ Hz}, 2\text{H}), 7.45-7.47 (\text{m}, 3\text{H}), 7.37-7.33 (\text{m}, 4\text{H}), 7.31-7.28 (\text{m}, 3\text{H}), 7.20-7.15 (\text{m}, 4\text{H}); \]
\[
\text{13C NMR (100 MHz, CDCl}_3): \delta = 199.4, 140.9, 138.0, 136.4, 135.4, 133.7, 130.2, 129.7, 128.8, 128.7, 128.5, 128.2, 128.1, 126.4. \text{ GC-MS (EI): calcd for C}_{21}\text{H}_{16}\text{O [M] 284.12, found 284.18. GC-MS (EI): calcd for C}_{21}\text{H}_{16}\text{O [M] 284.12, found 284.17.} \]

(E)-3-phenyl-1-(pyridin-3-yl)prop-2-en-1-one (Table 2, 3j)

The general procedure was applied to 1-(pyridin-3-yl)ethanone (55 mg, 0.5 mmol), dibenzylamine (480 µL, 2.5 mmol) at 120 ºC for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 10:1~5:1) to afford the title compound as a yellow solid (58 mg, 54% yield). 

\[
\text{1H NMR (400 MHz, CDCl}_3): \delta = 9.24 (\text{d}, J = 1.6 \text{ Hz}, 1\text{H}), 8.80 (\text{dd}, J = 4.8, 2.0 \text{ Hz}, 1\text{H}), 8.28 (\text{dt}, J = 8.0, 2.0 \text{ Hz}, 1\text{H}), 7.83 (\text{d}, J = 15.6 \text{ Hz}, 1\text{H}), 7.67-7.65 (\text{m}, 2\text{H}), 7.51-7.44 (\text{m}, 5\text{H}); \]
\[
\text{13C NMR (100 MHz, CDCl}_3): \delta = 189.3, 153.3, 149.9, 146.2, 136.1, 134.6, 129.8, 129.7, 129.0, 128.8, 128.7, 128.5, 128.2, 128.1, 126.4. \]
133.7, 131.2, 129.2, 128.8, 123.8, 121.6. GC-MS (EI): calcd for C\textsubscript{14}H\textsubscript{11}NO [M] 209.08, found 209.10.

(E)-3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one (Table 2, 3k)\textsuperscript{10}

The general procedure was applied to 1-(thiophen-2-yl)ethanone (54 µL, 0.5 mmol), dibenzylamine (480 µL, 2.5 mmol) at 120 °C for 24 h under N\textsubscript{2}. The crude product was purified by column chromatography on silica gel (petroleum ether/CH\textsubscript{2}Cl\textsubscript{2} 5:2~1:1) to afford the title compound as a yellow solid (79 mg, 74% yield). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ = 7.88 (s, 1H), 7.84 (d, J = 11.6 Hz, 1H), 7.70-7.64 (m, 3H), 7.45-7.41 (m, 4H), 7.18 (t, J = 4.4 Hz, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ = 182.2, 145.7, 144.2, 134.9, 134.0, 131.9, 130.7, 129.1, 128.6, 128.4, 121.9. GC-MS (EI): calcd for C\textsubscript{13}H\textsubscript{10}OS [M] 214.05, found 214.10.

(E)-1-(furan-2-yl)-3-phenylprop-2-en-1-one (Table 2, 3l)\textsuperscript{9}

The general procedure was applied to 1-(furan-2-yl)ethanone (50 µL, 0.5 mmol), dibenzylamine (480 µL, 2.5 mmol) at 120 °C for 24 h under N\textsubscript{2}. The crude product was purified by column chromatography on silica gel (petroleum ether/CH\textsubscript{2}Cl\textsubscript{2} 5:2~1:1) to afford the title compound as a yellow solid (53 mg, 54% yield). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ = 7.75 (d, J = 7.2 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.47-7.38 (m, 5H), 7.34 (m, 1H), 7.18 (s, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ = 199.5, 142.2, 138.5, 136.9, 135.8, 131.7, 129.7 (2C), 129.5 (2C), 128.6, 128.5 (2C). GC-MS (EI): calcd for C\textsubscript{13}H\textsubscript{10}O\textsubscript{2} [M] 198.07, found 198.12.
(2E,2'E)-1,1''-(1,4-phenylene)bis(3-phenylprop-2-en-1-one) (Table 2, 3m)\(^\text{10}\)

The general procedure was applied to 1,1''-(1,4-phenylene)diethanone 1d (81 mg, 0.5 mmol), dibenzylamine 2d (960 µL, 5.0 mmol), and (NH\(_4\))\(_2\)S\(_2\)O\(_8\) (685 mg, 3.0 mmol) at 120 °C for 24 h under N\(_2\). The crude product was purified by column chromatography on silica gel to provide the desired product (using petroleum ether/CH\(_2\)Cl\(_2\) 10:1~5:1 as mobile phase) as a yellow solid (51 mg, 30% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ = 8.13 (s, 4H), 7.85 (d, \(J = 15.6\) Hz, 2H), 7.68–7.66 (m, 4H), 7.54 (d, \(J = 15.6\) Hz, 2H), 7.46–7.44 (m, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ = 190.1, 145.9, 141.3, 134.6, 130.9, 129.1, 128.7, 128.6, 121.9. LC-MS (ESI\(^+\)): calcd for C\(_{24}\)H\(_{18}\)O\(_2\) [M+H]\(^+\) 339.14, found 339.24.

(2E, 6E)-2,6-dibenzylidenecyclohexanone (Table 2, 3n)\(^\text{11}\)

The general procedure was applied to cyclohexanone (52 µL, 0.5 mmol), dibenzylamine (480 µL, 5.0 mmol) at 120 °C for 24 h under N\(_2\). The crude product was purified by column chromatography on silica gel (petroleum ether/CH\(_2\)Cl\(_2\) 5:1~5:2) to afford the title compound as a yellow solid (71 mg, 52% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ = 7.80 (s, 2H), 7.45 (d, \(J = 7.2\) Hz, 4H), 7.38 (t, \(J = 7.6\) Hz, 4H), 7.31 (t, \(J = 7.2\) Hz, 2H), 2.90 (t, \(J = 5.2\) Hz, 4H), 1.80-1.74 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ = 190.5, 137.0, 136.3, 136.1, 130.5, 128.7, 128.5, 28.6, 23.1. GC-MS (EI): calcd for C\(_{20}\)H\(_{18}\)O [M] 274.14, found 274.19.

(\(E\))-3-(4-bromophenyl)-2-methyl-1-phenylprop-2-en-1-one (Table 3, 3o)\(^\text{12}\)

The general procedure was applied to propiophenone (33 µL, 0.25 mmol), 1-(4-bromophenyl)-N-methylmethanamine (250 µL, 1.25 mmol) at 120 °C for 24 h under N\(_2\). The crude product was purified by column chromatography on silica gel (petroleum ether/CH\(_2\)Cl\(_2\) 5:1~5:2) to afford the title compound as a light yellow solid.
(67 mg, 89% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.74$ (d, $J = 7.2$ Hz, 2H), 7.55-7.53 (m, 3H), 7.46 (t, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.2$ Hz, 2H), 7.09 (s, 1H), 2.24 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 199.2$, 140.6, 138.2, 137.5, 134.7, 131.8, 131.7, 131.2, 129.5, 128.3, 122.8, 14.5. GC-MS (EI): calcd for C$_{16}$H$_{13}$BrO [M] 300.01, found 300.07.

$(E)$-3-(2-bromophenyl)-2-methyl-1-phenylprop-2-en-1-one (Table 3, 3p)

The general procedure was applied to propiophenone (33 µL, 0.25 mmol), 1-(2-bromophenyl)-N-methylmethanamine (184 µL, 1.25 mmol) at 120 ºC for 24 h under N$_2$. The crude product was purified by column chromatography on silica gel (petroleum ether/CH$_2$Cl$_2$ 5:1~5:2) to afford the title compound as a light yellow solid (39 mg, 52% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.93$ (d, $J = 8.0$ Hz, 2H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.62 (t, $J = 7.6$ Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 2H), 7.42 (m, 2H), 7.32 (s, 1H), 7.26 (m, 1H), 2.17 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 199.1$, 140.7, 138.1, 137.9, 136.3, 132.8, 130.4, 129.74 (2C), 129.67 (2C), 128.3 (2C), 127.1, 124.2, 14.2. HRMS (ESI$^+$): calcd for C$_{16}$H$_{13}$BrO [M+Na]$^+$ 323.0047, found 323.0056.

$(E)$-3-(2-fluorophenyl)-2-methyl-1-phenylprop-2-en-1-one (Table 3, 3q)

The general procedure was applied to propiophenone (33 µL, 0.25 mmol), 1-(2-fluorophenyl)-N-methylmethanamine (166 µL, 1.25 mmol) at 120 ºC for 24 h under N$_2$. The crude product was purified by column chromatography on silica gel (petroleum ether/CH$_2$Cl$_2$ 5:1~5:2) to afford the title compound as a light yellow oil (30 mg, 50% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.79$ (d, $J = 8.0$ Hz, 2H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.49-7.42 (m, 3H), 7.36-7.31 (m, 1H), 7.21-7.17 (m, 2H), 7.10 (t, $J = 8.1$ Hz, 1H), 2.18 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 199.0$, 161.5, 159.0, 138.9, 138.1, 134.3 ($J = 12$ Hz), 132.0, 130.4, 129.6 (3C), 128.3 (2C), 123.9 ($J = 12$ Hz).
Hz), 115.7 (J = 22 Hz), 14.6. HRMS (ESI+): calcd for C_{16}H_{13}FO [M+Na]^+ 268.0848, found 263.0844.

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\begin{align*}
\text{(E)-3-(4-chlorophenyl)-2-methyl-1-phenylprop-2-en-1-one (Table 3, 3r)}^{13} \\
\text{The general procedure was applied to propiophenone (33 µL, 0.25 mmol), 1-(4-chlorophenyl)-N-methylmethanamine (179 µL, 1.25 mmol) at 120 °C for 24 h under N}_2. \text{ The crude product was purified by column chromatography on silica gel (petroleum ether/CH}_2\text{Cl}_2 \text{ 5:1~5:2) to afford the title compound as a light yellow oil (50 mg, 78% yield). } \text{^1H NMR (400 MHz, CDCl}_3): \delta = 7.73 (d, J = 8.4 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.2 Hz, 2H), 7.39-7.33 (m, 4H), 7.11 (s, 1H), 2.24 (d, J = 0.8 Hz, 3H); } \text{^13C NMR (100 MHz, CDCl}_3): \delta = 199.2, 140.6, 138.3, 137.4, 134.5, 134.2, 131.8, 130.9, 129.5, 128.7, 128.3, 14.5. GC-MS (EI): calcd for C_{16}H_{13}ClO [M] 256.07, found 256.12.}
\end{align*}
\]

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\begin{align*}
\text{(E)-2-methyl-1-phenyl-3-(p-tolyl)prop-2-en-1-one (Table 3, 3s)}^{14} \\
\text{The general procedure was applied to propiophenone (33 µL, 0.25 mmol), N-methyl-1-(p-tolyl)methanamine (184 µL, 1.25 mmol) at 120 °C for 24 h under N}_2. \text{ The crude product was purified by column chromatography on silica gel (petroleum ether/CH}_2\text{Cl}_2 \text{ 5:1~5:2) to afford the title compound as a colorless oil (45 mg, 75% yield). } \text{^1H NMR (400 MHz, CDCl}_3): \delta = 7.73 (d, J = 6.8 Hz, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 7.33 (d, J = 16 Hz, 2H), 7.21 (d, J = 16 Hz, 2H), 7.17 (s, 1H), 2.38 (s, 3H), 2.27 (s, 3H); } \text{^13C NMR (100 MHz, CDCl}_3): \delta = 199.6, 142.6, 138.9, 138.7, 136.0, 133.0, 131.5, 129.8, 129.5, 129.2, 128.2, 21.4, 14.4. GC-MS (EI): calcd for C_{17}H_{16}O [M] 236.12, found 236.17.}
\end{align*}
\]
(E)-3-(4-methoxyphenyl)-2-methyl-1-phenylprop-2-en-1-one (Table 3, 3t)

The general procedure was applied to propiophenone (33 µL, 0.25 mmol), 1-(4-methoxyphenyl)-N-methylmethanamine (195 µL, 1.25 mmol) at 120 ºC for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 5:1~5:2) to afford the title compound as a light yellow solid (43 mg, 67% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.70 (dd, J = 8.0, 1.6 Hz, 2H), 7.52 (t, J = 5.6 Hz, 1H), 7.45 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.15 (s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 2.28 (d, J = 1.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 199.6, 160.0, 142.7, 138.9, 134.9, 131.6, 131.4, 129.4, 128.4, 128.2, 114.0, 55.4, 14.4. HRMS (ESI⁺): calcd for C₁₇H₁₆O₂ [M+Na]⁺ 275.1048, found 275.1052.

(E)-3-(2-methoxyphenyl)-2-methyl-1-phenylprop-2-en-1-one (Table 3, 3u)

The general procedure was applied to propiophenone (33 µL, 0.25 mmol), 1-(2-methoxyphenyl)-N-methylmethanamine (188 µL, 1.25 mmol) at 120 ºC for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 5:1~5:2) to afford the title compound as light yellow oil (35 mg, 56% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.79 (d, J = 8.0 Hz, 2H), 7.53 (t, J = 7.2 Hz, 1H), 7.47-7.40 (m, 3H), 7.38 (s, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 3.80 (s, 3H), 2.18 (d, J = 1.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 199.4, 157.4, 138.7, 138.5, 136.4, 131.6, 130.1,130.0, 129.7, 128.1, 124.9, 120.2, 110.5, 55.5, 14.4. HRMS (ESI⁺): calcd for C₁₇H₁₆O₂ [M+Na]⁺ 275.1048, found 275.1047.
(E)-2-methyl-3-(3-nitrophenyl)-1-phenylprop-2-en-1-one (Table 3, 3v)

The general procedure was applied to propiophenone (33 µL, 0.25 mmol), N-methyl-1-(3-nitrophenyl)methanamine (179 µL, 1.25 mmol) at 120 ºC for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 5:1~5:2) to afford the title compound as a white solid (46 mg, 68% yield). ¹H NMR (400 MHz, CDCl₃): δ = 8.27 (t, J = 2.0 Hz, 1H), 7.78 (td, J = 8.0, 0.8 Hz, 1H), 7.77 (td, J = 8.4, 2.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.62-7.56 (m, 2H), 7.48 (t, J = 5.6 Hz, 2H), 7.16 (s, 1H), 2.28 (d, J = 1.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 198.7, 148.3, 139.5, 138.1, 137.7, 137.4, 135.2, 132.2, 129.5 (3C), 128.4 (2C), 124.1, 123.1, 14.6. HRMS (ESI⁺): calcd for C₁₆H₁₃NO₃ [M+Na]⁺ 290.0793, found 290.0789.

![Structure of (E)-2-methyl-3-(3-nitrophenyl)-1-phenylprop-2-en-1-one](image)

(E)-3-(4-cyanophenyl)-2-methyl-1-phenylprop-2-en-1-one (Table 3, 3w)

The general procedure was applied to propiophenone (33 µL, 0.25 mmol), 4-((methylamino)methyl)benzonitrile (176 µL, 1.25 mmol) at 120 ºC for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 5:1~5:2) to afford the title compound as a white solid (56 mg, 89% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.76 (d, J = 7.6 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.51-7.46 (m, 4H), 7.11 (s, 1H), 2.25 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 198.7, 140.3, 139.7, 138.7, 137.6, 132.5, 132.2, 130.0, 129.6, 128.4, 118.6, 111.8, 14.7. HRMS (ESI⁺): calcd for C₁₇H₁₃NO [M+Na]⁺ 270.0895, found 270.0933.

![Structure of (E)-3-(4-cyanophenyl)-2-methyl-1-phenylprop-2-en-1-one](image)

(E)-2-methyl-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one (Table 3, 3x)

S15
The general procedure was applied to propiophenone (33 µL, 0.25 mmol), N-methyl-1-(naphthalen-1-yl)methanamine (204 µL, 1.25 mmol) at 120 ºC for 24 h under N₂. The crude product was purified by column chromatography on silica gel (petroleum ether/CH₂Cl₂ 5:1~5:2) to afford the title compound as a white solid (33 mg, 48% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.88 (m, 4H), 7.80 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.58 (t, J = 6.4 Hz, 1H), 7.52 (m, 6H), 2.15 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 199.3, 140.3, 139.0, 138.5, 133.6, 133.0, 131.9, 131.4, 129.5, 128.9, 128.7, 128.4, 126.8, 126.5, 126.2, 125.2, 124.5, 14.6. HRMS (ESI⁺): calcd for C_{20}H_{16}O [M+Na]⁺ 295.1099, found 295.1093.

4. Concise Synthesis of Bioactive Cytotoxic Dihydrochalcone 4

\[ \text{OMe} \]
\[ \text{OMe} \]
\[ \text{OMe} \]
\[ \text{OMe} \]

Compound 1e, 1c were prepared according to the literature.¹⁵

1-(2-Hydroxy-4,6-dimethoxyphenyl)ethanone 1e: 947 mg, 90% yield. ¹H NMR (400 MHz, CDCl₃): δ = 14.03 (s, 1H), 6.05 (d, J = 2.4 Hz, 1H), 5.91 (d, J = 2.4 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.61 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 203.2, 167.6, 166.1, 162.9, 106.0, 93.5, 90.8, 55.6 (2C), 32.9.

1-(2,4-Dihydroxy-6-methoxyphenyl)ethanone 1c: 357 mg, 70% yield. ¹H NMR (400 MHz, DMSO-\(d^6\)): δ = 13.82 (s, 1H), 5.97 (d, J = 2.0 Hz, 1H), 5.86 (d, J = 2.0 Hz, 1H),
3.82 (s, 3H), 2.52 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ = 202.2, 166.3, 165.2, 163.4, 104.6, 95.6, 91.3, 55.8, 32.6.

**Synthesis of compound 3y:** The general procedure was applied to compound 1c (91 mg, 0.5 mmol), 1-(4-methoxyphenyl)-N-methylmethanamine 2f (390 µL, 2.5 mmol), and (NH$_4$)$_2$S$_2$O$_8$ (342.3 mg, 1.5 mmol) at 120 ºC for 24 h under N$_2$. The crude product was purified by column chromatography on silica gel to provide the desired product 3y as a yellow solid (80 mg, 55% yield) (using petroleum ether/ethyl acetate 5:1~5:2 as mobile phase). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 14.04 (s, 1H), 9.89 (s, 1H), 7.97 (d, $J$ = 15.6 Hz, 1H), 7.84 (d, $J$ = 15.6 Hz, 1H), 7.61 (d, $J$ = 6.8 Hz, 2H), 7.01 (d, $J$ = 8.4 Hz, 2H), 6.05 (d, $J$ = 2.4 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 189.8, 166.6, 165.1, 163.6, 161.9, 131.0 (2C), 128.9, 113.3 (2C), 105.0, 92.4 (2C), 89.7 (2C), 54.6, 54.5.

**Synthesis of cytotoxic dihydrochalcone 4:** In a dried Schlenk tube, compound (45 mg, 0.15 mmol), Pd/C (5 wt%, 20 mg) and ethanol (2.0 mL) were added under a hydrogen atmosphere (1.0 atm). The mixture was stirred at room temperature for overnight. After evaporation of the solvent under vacuum, the resulting residue was purified by chromatography (PE/EtOAc = 5:2) to provide the desired product 4 as a white solid (32 mg, 70% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 13.96 (s, 1H), 7.15 (d, $J$ = 8.8 Hz, 2H), 6.84 (d, $J$ = 8.4 Hz, 2H), 5.99 (d, $J$ = 2.4 Hz, 1H), 5.90 (d, $J$ = 2.4 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.26 (t, $J$ = 7.6 Hz, 2H), 2.93 (t, $J$ = 7.2 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 203.2, 167.6, 166.1, 162.9, 159.2, 133.1, 128.7, 114.0, 106.0, 93.5, 90.8, 55.6, 55.3, 45.1, 32.9.

**5. Synthesis of Flavonoid Derivative 5 via a One-Pot Operation**

In a dried Schlenk tube, 1-(2-hydroxyphenyl)ethanone 1d (136 mg, 1.0 mmol), N-methyl-1-phenylmethanamine 2b (682 µL, 5.0 mmol), CuI (38.2 mg, 0.2 mmol),
(NH₄)₂S₂O₈ (684 mg, 3.0 mmol) and tert-Amyl alcohol (2.0 mL) were added under a nitrogen atmosphere. The reaction mixture was stirred at 120 °C for 48 h. Then the crude product was purified by column chromatography (PE/EtOAc = 5:2) (177 mg, 79% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.94 (d, J = 8.0 Hz, 1H), 7.54-7.48 (m, 3H), 7.46-7.39 (m, 3H), 7.08-7.05 (m, 2H), 5.49 (dd, J = 10.8, 2.8 Hz, 1H), 3.10 (dd, J = 13.2, 3.6 Hz, 1H), 2.90 (dd, J = 14.0, 2.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 192.0, 161.6, 138.7, 136.2, 128.9, 128.8, 127.1, 126.2, 121.7, 121.7, 120.9, 118.2, 79.6, 44.7. GC-MS (EI): calcd for C₁₅H₁₂O₂ [M] 224.08, found 224.15.

6. Synthesis of Compounds 6 and 7 for Mechanistic Studies

Synthesis of β-Amino Ketone 6 and the Related Ammonium Salt 7

In a dried Schlenk, chalcone 3f (936 mg, 4.5 mmol), benzylamine (492 µL, 4.5 mmol), KF/NP phosphate catalyst¹⁷,¹⁸ and methanol (4.5 mL) was added under a nitrogen atmosphere. Then the mixture was stirred at room temperature for 24 h. The desired β-amino ketone 6 was obtained as a white solid through recrystallization from a PE/EtOAc solution (850 mg, 60% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.89 (d, J = 7.6 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.43-7.39 (m, 4H), 7.36 (t, J = 7.4 Hz, 2H), 7.30-7.25 (m, 5H), 7.23-7.21 (m, 1H), 4.34 (dd, J = 4.4, 4.0 Hz, 1H), 3.62 (q, J = 13.6, 13.2 Hz, 2H), 3.38-3.28 (m, 2H), 2.26 (brs, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 198.9, 143.3, 140.4, 136.9, 133.2, 128.7, 128.6, 128.3, 128.2, 128.1, 127.41, 127.37, 126.8, 58.6, 51.6, 47.4. LC-MS (ESI⁺): calcd for C₂₂H₂₁NO [M+H]⁺ 316.17, found 316.27.

A Schlenk tube was loaded with β-amino ketone 6 (470 mg, 1.5 mmol) and EtOAc (5 mL). When 0.05 M H₂SO₄ (4 mL) was dropped into the solution, a colorless solid was produced at the boundary phase. After filtration and dry under vacuum, the desired ammonium salt 7 was obtained as a colorless solid (607 mg, 98%¹⁹). ¹H NMR (400
19 MHz, CDCl$_3$): $\delta = 7.82$ (d, $J = 7.6$ Hz, 2H), 7.72 (t, $J = 7.2$ Hz, 2H), 7.45-7.27 (m, 11H), 4.64 (s, 1H), 7.24 (d, $J = 16.4$ Hz, 1H), 4.07-4.03 (m, 1H), 3.95 (d, $J = 13.6$ Hz, 1H), 3.61 (d, $J = 13.6$ Hz, 1H), 1.61 (brs, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 199.0$, 143.2, 140.4, 136.9, 133.2, 128.7, 128.6, 128.3, 128.2, 128.1, 127.43, 127.38, 126.8, 57.7, 48.4, 42.8. LC-MS (ESI$^+$): calcd for C$_{22}$H$_{21}$NO [M-HSO$_4$]$^+$ 316.17, found 316.21.

REFERENCES
7. Copies of $^1$H and $^{13}$C NMR spectra